Combination treatment for depressed outpatients: efficacy and prediction of outcome

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General Introduction

This thesis focuses on two questions: is a combination of psychotherapy and medication more effective in treating major depressive disorder (MDD) than either psychotherapy or medication alone. The second question concerned the prediction of outcome: do personality factors predict short term outcome in depression? In this field our special interest concerned the possible role of personality dimensions in the prediction of response to therapy.

A brief history of depression

Major depressive disorder (MDD) has for those afflicted a devastating impact on social and occupational functioning. Mankind has suffered from this illness since time immemorial. Descriptions of the affliction can be found in our earliest literature. For example the Bible describes Saul being left by God and suffering from an evil spirit. The young David was summoned to play his harp for him. This did help but later Saul took his own life (1 Samuel 31:1-13).

Efforts to understand, classify, and treat MDD go back almost as early. Hippocrates, in the 4th century B.C., saw all emotions as originating in the brain. The early Greeks attributed depression to an excess amount of black gall (hence the name 'melancholia', which is Greek for "black bile"). Subsequent philosophers, for instance Epicurus, saw an important interpersonal component in the origin of emotions (Solomon, 2001;Stone, 1997) describes how since the time of Plato and Hippocrates differences of opinion have existed about the origin and cure of depression: where Hippocrates can be seen as the grandfather of Prozac, Plato is the grandfather of psychodynamic psychotherapy.

In 1621 Robert Burton describes melancholia naming fear and sorrow as the main characteristics, which occur "without a cause" (p. 169). Further on he lists as "causes" for melancholia sins against God and one's fellow man, and fills his lengthy book with almost every kind of mishap as a possible cause, from disease and illness to bad diet, from discontent to thwarted ambition. Burton was also one of the first to draw a clear connection between loss of attachment and subsequent mood disorder (Brink,

1979). In this he can be seen as anticipating the work of Bowlby (1980).The duration of depression was considered in pre-modern times to be chronic (Rousseau, 2000). It was an affliction from which no escape was possible and was associated with a feeble character. In that sense some saw it as almost natural that women should be afflicted more than men (Rousseau, 2000).

The term “depression” is of much more recent origin than “melancholia”. It was used for the first time in the 18th century and is derived from the Latin”deprimere” (to press down) (Jackson, 1986).

Kraepelin (Stone, 1997) used the term melancholia to describe an illness much like the modern concept of MDD. He conceptualized it as distinct from dementia praecox, an illness distinguished by so-called “Verblödungsprozesse”. He saw the cause of melancholia in the majority of cases as hereditary because most often no independent causal agent could be found (Jackson, 1986). Kraepelin saw all depressive disorders as part of the manic-depressive spectrum.

Freud (1917) in his publication *Mourning and Melancholia*, which builds on the work of Carl Abraham (1911), differentiated between normal grief and depression. The difference was that normal grief was about the loss of a real person, whereas in melancholia the relationship was a complicated and ambivalent one, and was caused by “constitutional ambivalence or traumatic experiences in connection with the object” (Freud, 1917, p. 61).

The second biological revolution in the treatment of depression (the first, biological, revolution being the discovery of Treponema pallidum as the cause of dementia paralytica) came with the discovery of iproniazid (a monoamine oxidase (MAO)-inhibitor) in 1951 and the tricyclic antidepressant imipramine in 1957. These discoveries led to an interest in the role of neurotransmitters such as serotonin, noradrenalin, and dopamine in MDD. With the advent of modern antidepressants such as fluoxetine and nefazodone, with relative mild side effects, treatment became available for large groups of patients.

Research in psychotherapy

Modern classification as introduced in the Diagnostic and Statistical Manual of Mental Disorders 3rd edition (DSM-III (APA, 1980) and the International Classification of mental and behavioral disorders(1992), 10th edition (WHO, 1992) (ICD-10) made it possible to compare groups of patients across different treatments. Up until the seventies and eighties of the last century, psychoanalysis and its close cousin, psychodynamic psychotherapy, were almost the only forms of psychotherapy practiced. Data on the efficacy of these forms of psychotherapy were almost non-existent and limited to case histories. One of the first to systematically investigate the efficacy of psychotherapy was Aaron Beck. His cognitive theory of depression and the therapy that derives its name from this theory form one consistent whole (Beck, Rush et al., 1979). Shortly thereafter other forms of psychotherapy 'designed' for specific groups of patients or for a particular disorder were created. Although much less mentioned than the biological revolutions, these innovations certainly can be seen as a major advance in the field of psychiatry and nothing short of a revolution.

As recently as the 1970s (Bergin & Strupp, 1970) found that systematic effectiveness research in the field of psychotherapy was almost impossible because researchers and practitioners were generally unwilling to participate in efficacy research.

The US National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program (TDCRP) was one of the first major trials in psychotherapy to compare different forms of psychotherapy with medication (Elkin, Parloff et al., 1985). It showed that efficacy research on psychotherapy is in fact very feasible. The main outcome of this trial (Elkin, Shea et al., 1989) will be discussed in Chapter 4. Demonstrating that several forms of treatment for depression do indeed work was a major advance. Some believed that all forms of depression could now be treated. It was in this overly optimistic mood that the 20th century closed. Increasingly however, it has become clear that there are still major problems in the classification and the (long-term) treatment of depression. This is a more so(m)ber, but probably more realistic perspective.

The classification of depression

Before the publication of the DSM-III (APA, 1980), there were several diagnostic descriptions. For instance Kendell (1976) distinguished nine forms of depression. Of course many criteria used in the different diagnostic descriptions overlapped, and confusion was abundant. Moreover, different etiological conceptions (e.g. endogenous depression, menopausal depression) further confused the already expressionistic picture. The publication of the DSM-III (APA, 1980) introduced a detailed and standardized taxonomy. This was a major advancement in the field of psychiatry both for researchers and practitioners. Subsequent editions of the DSM have not advanced the situation. One of the major critiques of the DSM is that the distinction between normal sadness and pathological depression has become unclear (Van Praag, 2000). Depressive disorder is in all probability a group of syndromes or illnesses all gathered under the same name. Because of this, the results of randomized clinical trials are increasingly hard to compare, due to the broad spectrum of patients all gathered under the same denominator.

According to the DSM-IV (APA, 1994), a diagnosis of MDD is made if the patient manifests 5 or more of 9 symptoms (see Table 1) during a 2-week period. One of the first 2 symptoms must be present in order to make a diagnosis. Additional specifiers are recurrence of an episode and severity of the episode (mild, moderate or severe (with or without psychotic features), in complete or partial remission). While not coded, the clinician can specify the presence of melancholic, catatonic or atypical features. Chronic episodes (> 2years' duration) or post-partum onset can also be indicated separately.

Besides major depressive disorder the DSM-IV names several other depressive syndromes: dysthymic disorder, mood disorder due to a general medical condition or substance use, depressive disorder not otherwise specified. Depressive episodes in the course of a bipolar I or II illness are also classified separately.

Table 1: DSM-IV Criteria for Major Depressive Episode

A.	1. Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others. 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. 3. Significant weight loss or decrease or increase of appetite nearly every day. 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day. 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day. 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day. 9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan to commit suicide.
B.	The symptoms do not meet criteria for a Mixed episode.
C.	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D.	The symptoms are not due to the direct physiological effects of a substance or a general medical condition.
E.	The symptoms are not better accounted for by Bereavement.

The epidemiology of depression

MDD is a prevalent disorder in the community. A recent study in the US showed a lifetime prevalence of 16.6% (Kessler, Berglund et al., 2005) for MDD and 2.5% for dysthymia. This figure corresponds with the Dutch figure of 15% found in a major Dutch study (Bijl, van Zessen et al., 1997). Mean age of onset is around 30 years of age (Kessler et al., 2005) and as is consistently found, more women than men are afflicted. Compared to earlier studies (Kessler, McGonagle et al., 1994), the prevalence of MDD seems to be rising, at least in the US.

Overall the prognosis of MDD in the general population seems good. More than three quarters of those afflicted recover within 3 months. However for those that do not recover after three month, the prognosis is bleaker. About one fourth of patients suffering from MDD will not recover within one year (Spijker, Bijl et al., 2001). Twenty percent of patients will develop a chronic (>24 months) condition (Spijker, de Graaf et al., 2002).

Treatment of depression

In most studies the efficacy of various antidepressant medications for MDD is equal (NICE, 2003). This finding does however not apply to all forms of depression or to all patients. For instance, for psychotic depression tricyclic antidepressants are often found to be more effective than other classes of antidepressants, notably the selective serotonergic reuptake inhibitors (SSRI's) (Wijkstra, Lijmer et al., 2006), and in atypical depression MAO-inhibitors have been shown to be more effective than tricyclic antidepressants (Liebowitz et al., 1988; Quitkin et al., 1990).
Several guidelines (Multidisciplinaire Richtlijn Depressie, 2005; NICE, 2003) provide excellent overviews of the forms of treatment of MDD.

Psychotherapy

The forms of psychotherapy which are best studied in the treatment of MDD are cognitive or cognitive-behavior therapy (CBT) and interpersonal psychotherapy (IPT). Since IPT will be described in full in Chapter 2, we will not describe it here. CBT was developed by (Beck et al., 1979). CBT is a brief therapy primarily aimed at changing old and dysfunctional ways of thinking and replacing them with more adaptive ways. The patient is given homework after each session and encouraged to practice at home the skills learned in therapy. CBT is probably by far the most frequently practiced form of psychotherapy for depression in the Netherlands. There is enough proof to state that psychological therapies are effective in the treatment of MDD (Cuijpers & Dekker, 2005).

Pharmacotherapy

Since the discovery of imipramine, a tricyclic antidepressant, in 1957, numerous other substances have been found to be effective in the treatment of depression, the most important classes being the irreversible MAO-inhibitors, tricyclic antidepressants, and the SSRIs. Almost all known antidepressants increase the availability of one or more monoamine neurotransmitters thought to play a major role in MDD. The most

common is serotonin, but dopamine and noradrenalin have also been found to play a role in MDD.
More recently other forms of antidepressants have been developed, with as common factor the ability to influence aminergic receptors other than serotonin.
Some studies (Thase, Entsuah et al., 2001) have found evidence for one particular medication, but generally speaking, the efficacy of all antidepressants seems to be equal.

Combination treatment

Over time, a whole plethora of treatments have been developed for MDD, from running to bright light therapy, from electroconvulsive therapy to different forms of psychotherapy. Over time, many combinations have been tried and sometimes found to be effective (Fava & Rush, 2006). In this study only the combination of a specific form of psychotherapy (IPT) and a specific medication (nefazodone) will be examined. The reason we had for selecting this combination is threefold:
At face value, it seems a very logical thing to do. Both forms of treatment have been shown to be effective in the treatment of MDD. The mechanism of action of each is largely unknown, but it is likely to be different. Chances are therefore that psychotherapy and pharmacotherapy will be complementary.
If asked, many clinicians also see this combination as the treatment of choice. Although clinical preference cannot be the sole reason for choosing an intervention, one has to look closely at its merits before putting it aside. It could well be that this clinical preference is the main reason why combination treatment is recommended in guidelines (eg, APA, 2004).
The third reason was that we found that the combination, though popular among clinicians and patients, has been little studied. In the few studies we found (see Chapter 3), results were mixed with respect to the superior efficacy of combination treatment compared to medication or psychotherapy alone.

Prediction of outcome

One of the main aims of this study was to find a more broadly effective treatment for patients suffering from MDD. But even if we did find that the combination of psychotherapy and medication is more effective than single treatment, this would still not mean that we would be able to help every patient.

Finding clinically relevant predictors of short- and long-term outcome has up until now been a vexing problem. For a major part this is due to the very large number of potential predicting factors. Sociodemographic variables, illness-related variables, comorbidity, and personality factors, amongst others, can all be considered as possible predictors of treatment outcome. All have been investigated in varying degrees but no consistent pattern emerges. This is partly due to the question of what exactly is predicted: the development of MDD, the response to acute treatment, or the recurrence and relapse after recovery. Another part of the problem is methodological: to test adequately all or at least a substantial part of the prediction factors would entail having a large number of participants in the study.

In this study our special interest was in the role of personality factors as predictors for response to acute treatment. Interest in the connection between personality and MDD is of long standing but has gained momentum since the introduction of the Axis II of the DSM-III in 1980 (APA, 1980). There is an extensive literature on the relationship, often misnamed comorbidity, between personality disorder and MDD (Enns & Cox, 1997; Mulder, 2002).

Our interest was however not primarily in the role of personality disorders as possible predictors of outcome but rather in the dimensions or factors of personality in treatment outcome. There are many advantages of a model to describe personality in dimensional terms over a model such as the DSM , which uses categories to diagnose personality disorders (Clark, 2005; Verheul, 2005). The validity of the current Axis II has come increasingly under fire. For instance, the most frequently diagnosed personality disorder is “personality disorder not otherwise specified” (Verheul & Widiger, 2004), in which persons have symptoms from a variety of personality

disorders. Besides validity, reliability has also been found to be an issue in the current system of personality disorders (Clark, 2005).

A dimensional model describes more accurately the continuum between normality and pathology and has advantages in the precision with which it describes behavior.

There are currently several models to describe normal personality. The most popular is the Five Factor Model (FFM) based on Eysenck's work (Eysenck & Eysenck, 1959) and that of Costa and McCrae (1992). The five factors or dimensions (hereafter called factors) used in the model by Costa and McCrae are Neuroticism (Ne), Extraversion (E), Openness to experience (O), Agreeableness (A), and Conscientiousness (C). Of these five factors, Ne has most often been related to MDD, E to a lesser extent, and where studied, the other three factors have not been found to be strongly related to either onset or course of MDD.

The relationship between personality factors and MDD is a complex one. According to Enns and Cox (1997), four kinds of relationships can be distinguished: vulnerability (personality factors predispose to the development of depression), pathoplasty (personality factors affect the expression of MDD), scarring (MDD leads to changes in personality function), and lastly, a spectrum or continuity model where an underlying process is thought to be responsible for both personality and MDD.

Neuroticism

As stated above, of the five personality factors, Ne has been studied the most (Enns & Cox, 1997; Mulder, 2002). It has become clear that in depressed patients Ne is overall higher compared to normal controls, that Ne scores rise during a depressive episode (Ormel, Oldehinkel et al., 2004) and gradually decline during remission from an episode of MDD, but remain higher compared to normal controls (Ormel et al., 2004). Elevated Ne scores also predispose to subsequent new episodes of depression (Ormel et al., 2004).

The role of Ne in the short term outcome of treatment has not been studied much (Mulder, 2002).

Since Ne generally describes the way in which a person reacts when confronted with adverse events, it is possible that persons with high Ne profit differentially from psychotherapy as compared to medication.
Measuring Ne during an episode of major depression can however be difficult. There is clear evidence that depression influences Ne scores (Griens, Jonker et al., 2002; Hirschfeld, Klerman et al., 1983b). If change in the severity of personality factors can only be viewed as an epiphenomenon of depression then clearly they could not predictors of outcome. For this reason we measured personality factors before and after treatment. This would enable us to see if personality factors change in the same degree as depression scores.

Aims of the study

With the advent of modern antidepressive medication and effective forms of psychotherapy, it was hoped that MDD would be a treatable illness. More recent research has however pointed out that for many patients this is not the case. For instance Keitner, Ryan et al. (2006), calculated that a substantial minority of patients (20-40%) do not have a favorable response to standard therapy. Outside of controlled studies this figure may be much higher; for instance in one large study (Trivedi, Rush et al., 2006) the remission rate was 28%, and in a study by Rush, Trivedi et al. (2004) carried out with public sector patients, only 5% of patients reached remission within one year. Since many patients do not seem to recover after standard outpatient treatment, finding more effective treatments is very important. One of the common strategies is combining different forms of effective treatments into one package, not unlike the treatment of cancer, in which a combination of treatment (cytostatic drugs, radiation therapy), either simultaneously or sequentially, is the rule rather than the exception. We asked ourselves if a combination of two effective forms of treatment combined would in the short term be more effective in treating MDD than either treatment alone.
Furthermore, we felt that not all patients would profit equally from treatment. It is clinical lore that certain types of patients profit more from psychotherapy whereas

others should be treated with biological methods. To be able to predict accurately a priori who will profit from what form of therapy is important. The clinician has to date almost no evidence on which to base a considered choice for psychotherapy, pharmacotherapy or a combination. The second part of our study is therefore devoted to the quest for finding general (for all depressed patients together) and differential (what works best for whom) predictors of outcome.

Scope of the thesis

Chapter 2 gives an overview of the conceptual and methodological problems in the study of combination therapy with depressed outpatients. It concludes with recommendations for future studies (including our own) in this area. This chapter is a translation of an earlier publication in Dutch (Blom, Jonker et al., 2000b).

Chapter 3 is a critical review of the literature on combination therapy in MDD. This chapter is a translation and an update of an earlier publication in Dutch (Blom, Jonker et al., 2000a).

Chapter 4 describes interpersonal psychotherapy, the form of psychotherapy used in this study. The chapter gives an overview of the available evidence for the efficacy of IPT and concludes with some considerations on the question why IPT is efficacious in the treatment of MDD. The chapter is a combination and expansion of a reedited chapter of an earlier publication in Dutch (Blom & Jonker, 2005b) and a chapter in an upcoming book (Weissman & Blom).

Chapter 5 reports the findings of the efficacy study involving four treatment conditions, nefazedone, IPT, IPT with nefazodone, and IPT with placebo. In this study we screened 355 patients referred for treatment. Of these, 193 were randomized after screening over the four conditions and treated for 12 to 16 weeks. Measurement of severity was carried out at baseline, after 6 weeks of treatment, and at endpoint.

Chapter 6 looks into the stability of the Five Factor Model (FFM) across the duration of the treatment study. The FFM, as measured in this study by the NEO-Five Factor Inventory, was administered at baseline and on completion of treatment. The chapter

describes the five forms of continuity: structural, absolute, individual-level, ipsative, and differential continuity. Because we were able to collect data from a substantial number of participants, we could study all five forms of continuity across time and across different treatments. These five forms were calculated for both an expert-rated instrument for the assessment of the severity of depression, the Hamilton Depression Rating Scale (Hamilton, 1960), and a self-rating scale, the Beck Depression Inventory (Beck, Ward et al., 1961).

Chapter 7 deals with both general predictors of outcome and differential predictors for specific treatment condition as investigated in this study. It has a special focus on the role of personality factors in the overall and differential prediction of outcome in the treatment of depression.

Chapter 8 is a post hoc analysis of the subgroup of patients of non-Western origin. In the Netherlands, as in most other Western countries, large numbers of immigrants have entered the country in the last decades. From several reports (RvV, 2000) it has become clear that health care delivery, acceptance of treatment, and outcome may be worse in immigrant populations. It is not clear if treatments that are effective for the native population are also effective for ethnic minority patients.

Chapter 9 is a summary of the main findings of this thesis and concludes with a general discussion of the study results and suggestions for further research and directions for clinical practice.

The final chapter is a **summary** of the thesis in Dutch. This thesis concludes with words of gratitude to all whom have contributed, a currilum vitae and a list of publications by the author.